# EXHIBIT 7

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United States District Court,
D. New Jersey.

In re FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION.
Bernadette Glynn and Richard Glynn, Plaintiffs,
v.
Merck Sharp & Dohme Corp, Defendant.

Civil Action Nos. 11–5304, 08–08.
|
April 10, 2013.

**Attorneys and Law Firms**

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OPINION

PISANO, District Judge.

*1 Plaintiffs Bernadette Glynn and Richard Glynn ("Plaintiffs") bring this lawsuit against Defendant Merck, Sharp, & Dohme Corp. ("Defendant"), which manufactures Fosamax, a drug approved by the United States Food and Drug Administration ("FDA") for the treatment and prevention of osteoporosis. This matter is part of the multi-district litigation concerning Fosamax and involves allegations that Fosamax causes atypical femur fractures ("AFFs [1] ") and that it caused Plaintiff Mrs. Glynn ("Mrs.Glynn")'s femur fracture. Presently before the Court is Defendant's Omnibus *Daubert* Motion to exclude the expert testimony of Dr. Charles N. Cornell ("Dr.Cornell"), Dr. Michael J. Klein ("Dr.Klein"), Dr. David Madigan ("Dr.Madigan"), and Dr. Cheryl Blume ("Dr.Blume") as well as a motion to exclude the causation testimony of the treating physicians—Dr. Robert Busch ("Dr.Busch"), Dr. Robert Lindsay ("Dr.Lindsay"), Dr. Frederick Fletcher ("Dr.Fletcher"), and Dr. Britton Limes ("Dr.Limes") [docket # 28]. This Court heard oral argument on February 21, 2013 and April 2, 2013. For the reasons outlined below, the Motion is denied as to Drs. Cornell, Klein, Madigan, and Blume. The treating physicians' causation testimony will not be excluded if their opinions are based on their treatment and care of Mrs. Glynn.

**I. DISCUSSION**

Federal Rule of Evidence 702 provides that a witness

> qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:
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> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
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> (b) the testimony is based on sufficient facts or data;
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> (c) the testimony is the product of reliable principles and methods; and
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> (d) the expert has reliably applied the principles and methods to the facts of the case.

This Rule requires the proponent of expert testimony to show the "requisite 'qualifications, reliability, and fit' " or in other words, that "(1) the witness is qualified as an expert in a particular field; (2) the methodology applied by the witness is sufficiently reliable; and (3) the witness's testimony 'fits' the facts of the case in dispute—that is, the proffered testimony would assist the trier of fact." *Jones v. Synthes USA Sales, LLC*, 2010 WL 3311840, *4 (D.N.J. Aug.19, 2010); *see also McNamara v. Kmart Corp.*, 380 Fed. Appx. 148, 151 (3d Cir.2010); *Meadows v. Anchor Longwall & Rebuild, Inc.*, 306 Fed. Appx. 781, 788 (3d Cir.2009); *Pineda v. Ford Motor Co.*, 520 F.3d 237, 244 (3d Cir.2008); *Schneider ex rel. Estate of Schneider v. Fried*, 320 F.3d 396, 404 (3d Cir.2003).

First, the expert must be qualified; this requirement is interpreted liberally and "a broad range of knowledge, skills, and training qualify an expert as such." *In re Paoli R.R. Yard PCB Litigation*, 35 F.3d 717, 741 (3d Cir.1994).

*2 Second, "an expert's testimony is admissible so long as the process or technique the expert used in formulating the opinion is reliable." *Id.* at 742. An expert's opinion is reliable if it is "based on 'good grounds,' i.e., if it is based on the methods and procedures of science." *Id.* at 744. This inquiry requires a court to examine the "scientific validity and thus the evidentiary relevance and reliability [ ] of the principles that underlie a proposed submission" and to focus "solely on principles and methodology, not on the conclusions ... [the expert] generate[s]." *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 594–95, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993). In *Daubert*, the Supreme Court outlined several factors that a court may take into consideration in determining reliability, including whether the hypothesis can be tested, whether the methodology "has been subjected to peer review and publication," the methodology's rate of error, "the existence and maintenance of standards controlling the technique's operation," and whether there is general acceptance in the scientific community. *Id.* at 593–94. The proponent of the expert testimony must demonstrate that the opinions are reliable by a preponderance of the evidence. *In re Paoli*, 35 F.3d at 744.

Third, expert testimony "must fit the issues in the case" or in other words, "be relevant for the purposes of the case and must assist the trier of fact." *Schneider*, 320 F.3d at 404. The Court must determine "whether [the] expert testimony proffered ... is sufficiently tied to the facts of the case that it will aid the jury in resolving a factual dispute." *United States v. Schiff*, 602 F.3d 152, 173 (3d Cir.2010). This standard "is not that high" but "higher than bare relevance." *In re Paoli*, 35 F.3d at 745.

The Court's role, at a *Daubert* hearing, is to act "as a gatekeeper, preventing opinion testimony that does not meet the requirements of qualification, reliability and fit from reaching the jury." *Schneider*, 320 F.3d at 404. In keeping with its gatekeeping role, this Court will apply the *Daubert* analysis to each expert.

**A. Dr. Cornell**

Plaintiffs offer Dr. Cornell, an orthopedist, as an expert in causation, to establish that Fosamax causes AFFs and Mrs. Glynn's Fosamax use caused her AFF.

**1. Dr. Cornell Is Qualified as an Expert**

Dr. Cornell is currently a Professor of Clinical Orthopedic Surgery at Weill Cornell College of Medicine and has been the Richard Laskin Chair in Orthopedic Surgery since 2011 [docket # 102, Ex. 8, Dr. Cornell's Report ("Cornell Report") at 2]. In addition, Dr. Cornell is an attending orthopedic surgeon at the Hospital for Special Surgery in New York City and currently serves as the hospital's Director of the Department of Orthopedic Surgery. *Id.* He is a "specialist in orthopedic trauma ... and metabolic bone disease," which includes osteoporosis and osteopenia [docket # 102, Ex. 10, Dr. Cornell's Deposition ("Cornell Dep.") at 69:13–16; 71:14–17]. About 80% of all the fractures Dr. Cornell treats surgically are fractures "as a consequence of osteoporosis or osteopenia." *Id.* at 72:6–21. He has treated two patients with atypical fractures related to bisphosphonate use. Cornell Report at 3. Moreover, he has "participated in a study to determine a management strategy for the treatment of symptomatic bisphosphonate-associated incomplete atypical femoral fractures, which was peer reviewed and published in the Hospital for Special Surgery Journal." *Id.* Although Defendant argues that Dr. Cornell is not qualified because he is not trained in epidemiology and is unfamiliar with "the most basic epidemiological terms and concepts" (Db13[2]), Dr. Cornell does not have to possess a particular subspecialty—epidemiology—to testify as an expert. *See Schneider*, 320 F.3d at 406–07 (determining that testimony was improperly excluded because an individual "was not an expert in the sub-specialty about which he opined"); *Holbrook v. Lykes Bros. S.S. Co., Inc.*, 80 F.3d 777, 783 (3d Cir.1996) (declaring that the lower court erred by requiring the expert to have a particular specialization and "exact background"); *see also Keller v. Feasterville Family Health Care Ctr.*, 557 F.Supp.2d 671, 675 (E.D.Pa.2008) (recognizing that expert testimony cannot be excluded because "the expert is without the appropriate specialization" and that "[a] certain degree of background is not required"). Because Dr. Cornell has the academic background and professional experience with osteoporosis, osteopenia, and fractures associated with those diseases, he is qualified to testify as an expert in this case. *See Schneider*, 320 F.3d at 407.

**2. Dr. Cornell's Methodology Is Sufficiently Reliable**

*3 Dr. Cornell formed his opinion using the Bradford Hill criteria, which are "nine factors widely used in the scientific community to assess general causation." *Gannon v. United Sates*, 292 Fed. Appx. 170, 173 (3d Cir.2008);

Cornell Dep. at 329:5–8. General causation is when "an observed association between a chemical and a disease is causal." *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F.Supp.2d 584, 592 (D.N.J.2002), *aff'd*, 68 Fed. Appx. 356 (3d Cir.2003). The nine Bradford Hill factors are: "1. Temporal Relationship, 2. Strength of the association, 3. Dose-response relationship, 4. Replication of the findings, 5. Biological plausibility (coherence with existing knowledge), 6. Consideration of alternative explanations, 7. Cessation of exposure, 8. Specificity of the association, and 9. Consistency with other knowledge." FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, at 599–600 (3d ed.2011), *available at* http://www.fjc.gov/public/pd f.nsf/lookup/SciMan3D01.pdf/$file/SciMan3D01.pdf; *see also Gannon*, 292 Fed. Appx. at 173 n. 1; *In re Avandia Mktg., Sales Practices & Products Liab. Litig.*, 2011 WL 13576, *3 (E.D.Pa. Jan.4, 2011); *Magistrini*, 180 F.Supp.2d at 592–93. "[O]ne or more of the factors may be absent even where a causal relationship exists and ... no factor is a sine qua non of causation. *Magistrini*, 180 F.Supp.2d at 593 n. 9.

Dr. Cornell used the Bradford Hill criteria to form an opinion on whether Fosamax causes AFFs. Cornell Dep. at 331:4–8; Cornell Report at 4. In applying the nine Bradford Hill factors, he reviewed Plaintiff's medical records from 1996 to present, the office notes and depositions of her treating physicians, and "past and current medical literature on the topics of osteopenia, osteoporosis and their prevention and treatment with bisphosphonate drugs including alendronate," particularly publications concerning the FIT and FLEX studies and that described the appearance of AFFs. Cornell Report at 3, 4–5. He "review[ed] the original trials, the randomized trials, that led to the approval of Fosamax for the treatment of osteoporosis, and then wanted to review many of the case reports, the case series, the summed analysis, and some of the review papers that took all of this information and put it into a more readily digestible form." Cornell Dep. at 56:13–23. Dr. Cornell attempted to "present a balanced analysis" and pointed out studies on both sides of the issue. *Id.* at 58:5–16. He concluded that Fosamax can cause AFFs and "Fosamax use was a substantial contributing factor to Mrs. Glynn's femur fracture." Cornell Report at 4. The methodology Dr. Cornell used is sufficiently reliable because the Bradford Hill criteria are "broadly accepted" in the scientific community "for evaluating causation," *Gannon*, 292 Fed. Appx. at 173 n. 1, and "are so well established in epidemiological research," *In re Avandia Mktg. ., Sales Practices & Products Liab. Litig.*, 2011 WL 13576, at *3.

***4** Defendant, however, argues that Plaintiffs do not explain the scientific methodology used by Dr. Cornell or show that his methodology is sufficiently reliable. Instead, Defendant asserts that Dr. Cornell's "weight-of-the-evidence" methodology just lists some studies, only some of which support causation, and concludes that the weight of the evidence shows that Fosamax causes AFFs. Defendant explains that this method is inadequate because Dr. Cornell does not discuss how these studies establish causation or why certain studies outweigh others that do not find causation. Additionally, Defendant points out that Dr. Cornell has not done an evaluation of possible biases or confounding factors found in the studies. Because Dr. Cornell does not show that his methodology is sufficiently reliable to show general causation, Defendant argues that he cannot establish specific causation—that Mrs. Glynn's Fosamax use caused her AFF. Defendant explains that the Bradford Hill criteria do not apply to specific causation, and Dr. Cornell's differential diagnosis was unreliable because he did not rule out the possibility that other things could have caused Mrs. Glynn's fracture.

Defendant is free to address these issues on cross-examination, but Defendant's concerns do not prohibit Dr. Cornell from testifying as an expert because he is qualified and the methodology he used is sufficiently reliable. *See Milward v. Acuity Specialty Products Group, Inc.*, 639 F.3d 11, 15 (1st Cir.2011), *cert. denied*, —— U.S. ——, 132 S.Ct. 1002, 181 L.Ed.2d 734 (2012) (stating "*Daubert* does not require that a party who proffers expert testimony carry the burden of proving to the judge that the expert's assessment of the situation is correct"; instead, the "proponent of the evidence must show only that 'the expert's conclusion has been arrived at in a scientifically sound and methodologically reliable fashion.' ").

Regarding Dr. Cornell's specific causation opinion that Fosamax caused Mrs. Glynn's femur fracture, he applied the differential diagnosis method, which is "a technique that involves assessing causation with respect to a particular individual." *Kannankeril v. Terminix Int'l, Inc.*, 128 F.3d 802, 807 (3d Cir.1997). It "is a process by which a physician rules out alternative causes through review of a patient's medical histories and

records, physical examination of the patient, laboratory testing, study of relevant medical literature, and other techniques." *In re Diet Drugs (Phentermine/Fenfluramine/Dexfenfluramine) Products Liab. Litig.*, 890 F.Supp.2d 552, 561 (E.D.Pa.2012). The "technique is generally accepted in the medical community." *Id.*

Here, Dr. Cornell applied the differential diagnosis method by examining Mrs. Glynn's past medical history and conducting his own examination of her on September 26, 2012, after which he concluded that "[t]o a reasonable degree of medical certainty, Mrs. Glynn suffered a nontraumatic [AFF] in the setting of seven years of full dose Fosamax and alendronate therapy." Cornell Report at 34–36. Dr. Cornell reviewed radiographs taken on April 17, 2009 to evaluate the fracture and reviewed follow-up X-rays, hospital records, rehabilitation records, orthopedics records, prescription records from pharmacies, and deposition transcripts, among other things, in forming his opinion [docket # 109, Ex. 78, Appendix B to Cornell Report]. He ruled out possible alternative causes of Mrs. Glynn's AFF. Cornell Report at 38–40, 42–43, 45–46. Dr. Cornell did not have to "rule out every possible alternative cause of" Mrs. Glynn's AFF; instead, only "[o]bvious alternative causes need to be ruled out." *Heller v. Shaw Indus., Inc.*, 167 F.3d 146, 156 (3d Cir.1999). Thus, Dr. Cornell applied the differential diagnosis method in arriving at his conclusion that Mrs. Glynn's Fosamax use was a substantial contributing factor to her AFF.

*5 Therefore, the methodology used by Dr. Cornell in arriving at both his general and specific causation opinions is sufficiently reliable. Both the Bradford Hill criteria and differential diagnosis are widely used and accepted in the scientific community to arrive at causation opinions.

**3. Dr. Cornell's Testimony Fits the Facts of the Case**

Finally, Dr. Cornell's testimony fits the facts of the dispute and will assist the trier of fact because Plaintiffs seek to show that Mrs. Glynn's AFF was caused by her Fosamax use and Dr. Cornell not only opines that AFFs are caused by long term bisphosphonate use, like Fosamax, but also that Mrs. Glynn's Fosamax use was a "substantial contributing factor to her" AFF. *See* Cornell Report at p. 22, 47. Consequently, Dr. Cornell's proffered testimony will assist the trier of fact in determining whether Fosamax caused Mrs. Glynn's AFF.

Because Dr. Cornell is qualified, used a methodology that is sufficiently reliable, and his opinion fits the facts of a case, his expert testimony is admissible under *Daubert*.

**B. Dr. Klein**

Plaintiffs asked Dr. Klein, a pathologist, to offer his opinion on whether Fosamax use causes AFFs and the "mechanism by which those fractures are precipitated" [docket # 103, Ex. 11, Dr. Klein's Report ("Klein Report") at 2].

**1. Dr. Klein Is Qualified as an Expert**

Dr. Klein is currently the Director of Pathology and Laboratory Medicine at the Hospital for Special Surgery where he has "direct clinical responsibilities for patients ...." *Id.* at 3–4. He also has "direct clinical responsibilities ... as a consultant at Memorial Sloan–Kettering Cancer Center, and as an outside counsel for leading pathology laboratories at major hospitals and institutions around the country." *Id.* at 4. Dr. Klein has reviewed the pathology for at least four patients with AFFs [docket # 105, Ex. 37, Dr. Klein's Deposition ("Klein Dep.") at 41:4–12]. Dr. Klein is currently a Professor of Pathology and Laboratory Medicine at Weill Cornell Medical College. Klein Report at 3. He is involved with several publications, including as the lead author and editor of *Non-neoplastic Diseases of Bones and Joints*, the only peer-reviewed, comprehensive textbook on the issue, and as a member of the editorial boards of *Human Pathology*, *Skeletal Radiology*, *Advances in Anatomical Pathology*, and *HSS Journal*. *Id.* Dr. Klein is the Consultant Editor of Research for *The Journal of Bone and Joint Surgery (American)* and has authored or co-authored more than 180 articles, most of which relate to bone pathology. *Id.* Therefore, Dr. Klein possesses "a broad range of knowledge, skills, and training" to qualify him as an expert in pathology. *In re Paoli*, 35 F.3d at 741.

**2. Dr. Klein's Methodology Is Sufficiently Reliable**

Like Dr. Cornell, Dr. Klein used the Bradford Hill criteria to form his opinion. Klein Report at 2. As discussed above, the Bradford Hill methodology is sufficiently reliable because it is "widely used in the scientific community to assess general causation." *Gannon*, 292 Fed. Appx. at 173. In applying the nine Bradford Hill criteria, Dr. Klein reviewed human and animal studies

and studies performed by Defendant to form his opinion. *See* Klein Report at19–38. The studies revealed a strong association between bisphosphonates, like Fosamax, and microdamage in the bones as well as decreased bone toughness. *See id.* at 20, 25–30, 32. In addition, Dr. Klein noted a strong association between delayed fracture healing, due to altered bone quality, in patients and animals taking bisphosphonates. *Id.* at 23–24, 29. These findings were replicated in several studies discussed in Dr. Klein's report. Moreover, Dr. Klein cited one study which recognized the "*duration*-dependent, as well as dose-dependent, effect bisphosphonates have on the skeleton." *Id.* at 27. Another study mentioned in Dr. Klein's report noted that the "cessation of bisphosphonate treatment may be prudent for women on therapy who sustain a nonvertebral fracture." *Id.* at 30. Thus, Dr. Klein applied the Bradford Hill criteria, including the strength of association, replication of findings, dose-response relationship, and cessation of exposure factors.

*6 Based on his review of the studies, Dr. Klein concluded that "alendronate significantly alters the cellular properties of bisphosphonate-treated bone." *Id.* at 38. AFFs are not

> attributed to low bone mass or osteoporosis alone, indicative of bone that has fundamentally compromised bone microstructure. Unless a damaging force exerts tension across the entire cortex, the laws of physics and biomechanics as applied to bone further support the conclusion that bone quality and microstructure must be fundamentally compromised for a transverse fracture in a hollow cylinder[, like the femur,] to follow.
>
> [*Id.*]

Thus, Dr. Klein opined that there is a causal relationship between Fosamax and AFFs. *Id.* at 2. He used a sufficiently reliable methodology, the Bradford Hill criteria, in forming this opinion.

Defendant, however, argues that the Bradford Hill criteria apply to epidemiology studies, which Dr. Klein's report does not discuss. Defendant contends that Dr. Klein has not provided support for the proposition that a general causation conclusion can be established using the Bradford Hill criteria and human or animal biopsy data. In addition, Defendant asserts that if Dr. Klein discussed epidemiology studies in his report, he did not demonstrate that he is qualified to interpret that evidence because he has no expertise in epidemiology and does not understand the most basic epidemiology terms. Moreover, Defendant points out that Dr. Klein conceded that the mechanism regarding how bisphosphonates cause AFFs has not been established and that the theories Dr. Klein uses to support his conclusion about mechanism—microdamage, decrease in tissue heterogeneity, bone brittleness, and delayed healing—have not been proved with human data.

Yet, Dr. Klein has properly applied the Bradford Hill criteria to epidemiological studies. Epidemiological studies include randomized trials in which one group is exposed to an agent, such as Fosamax, and another group is not, and the effect of the agent or lack thereof is observed. FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE at 555–56. Here, Dr. Klein examined randomized trials, such as Dempster et al., Boskey et al., and Donnelly et al.; in each of these studies, some women were given alendronate or another bisphosphonate and others were not. Klein Report at 20–21. Moreover, the Federal Judicial Center's Reference Manual on Scientific Evidence states that "toxicology models based on live animal studies ... may be used to determine toxicity in humans" in addition to observational epidemiology. FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, at 563.

For his testimony to be admissible, Dr. Klein is not required to show that the mechanism has been definitely established. Instead, he just needs to show that the methodology he used to arrive at his opinion is sufficiently reliable. *See Milward,* 639 F.3d at 15 (stating "*Daubert* does not require that a party who proffers expert testimony carry the burden of proving to the judge that the expert's assessment of the situation is correct"; instead, the "proponent of the evidence must show only that 'the expert's conclusion has been arrived at in a scientifically sound and methodologically reliable fashion.' "). Dr. Klein arrived at his opinion on the mechanism by examining several studies and using a scientific method that is sufficiently reliable.

**3. Dr. Klein's Testimony Fits the Facts of the Case**

*7 Lastly, Dr. Klein's testimony fits the facts of the dispute and will assist the trier of fact. *See Jones,* 2010 WL 3311840, at *4. Through Dr. Klein's testimony, Plaintiffs seek to show that Fosamax causes AFFs and

the mechanism by which this happens. *See* Klein Report at 2. Dr. Klein opines that Fosamax causes AFFs and discusses several ways this happens—microdamage, abnormal osteoclasts, altered bone quality, and delayed fracture healing. Thus, Dr. Klein's testimony will assist the trier of fact in determining whether Fosamax causes AFFs, the ways in which this happens, and ultimately, his testimony will aid the jury in deciding whether Mrs. Glynn's Fosamax use caused her AFF.

**C. Dr. Madigan**

Plaintiffs asked Dr. Madigan, a statistician, to give his opinion regarding "whether a signal of problematic oversuppression of bone turnover and associated [AFF] ... existed for Fosamax, using industry standard pharmacovigilance techniques and data sources, and the adverse event terms selected by Merck to internally evaluate the same" and "assess the strength of that signal, if any, in comparison to the signal, if any, for such events in other products indicated for the prevention and treatment of osteoporosis" [docket # 33, Ex. 30, Dr. Madigan's Report ("Madigan Report") at ¶ 5].

**1. Dr. Madigan Is Qualified as an Expert**

Dr. Madigan is Professor and Chair of Statistics at Columbia University. *Id.* at ¶ 1. He is an elected Fellow of the Institute of Mathematical Statistics and the American Statistical Association, and from 1995 to 2005 was the 36th most cited mathematician worldwide. *Id.* In 2010, he completed a term as Editor of the journal *Statistical Science*. *Id.* Dr. Madigan has consulted for companies such as Novartis, Pfizer, and Sanofi–Aventis on several issues, "many related to drug safety." *Id.* at ¶ 2. He has statistical experience with clinical trials and has published more than 100 technical papers on many topics, including pharmacovigilance[3]. *Id.*

Within the last few years, drug safety "with a focus on the development and application of statistical methods for pharmacovigilance" has been "one of [Dr. Madigan's] significant research interests ...." *Id.* at ¶ 3. He has published work in several journals, including *Drug Safety, Pharmacoepidemiology and Drug Safety,* and *Epidemiology*. *Id.* Dr. Madigan is an investigator in the Mini–Sentinel project, which is "a pilot project sponsored by the FDA to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products." *Id.* He is the "methods lead for the Observational Medical Outcomes Partnership, a public-private partnership between the FDA and the pharmaceutical industry, which addresses "research methods that are feasible and useful to analyze existing healthcare databases to identify and evaluate safety and benefit issues of drugs already on the market." *Id.* Dr. Madigan is a member of the FDA's Drug Safety and Risk Management Committee, which "advises the FDA Commissioner on risk management, risk communication, and quantitative evaluation of spontaneous reports for drugs for human use and for any other product for which the FDA has regulatory responsibility." *Id.* Dr. Madigan is qualified as an expert because he has "a broad range of knowledge, skills, and training [to] qualify ... [him] as such." *In re Paoli,* 35 F.3d at 741. Defendant does not dispute Dr. Madigan's qualifications.

**2. Dr. Madigan's Methodology Is Sufficiently Reliable**

*8 Dr. Madigan examined the FDA's Adverse Event Reporting System ("AERS") database for a "possible association between Fosamax and a series of ... terms selected by Merck to evaluate oversuppression of bone turnover and associated" AFFs. Madigan Report at ¶ 25. The terms were: bone development abnormal, bone disorder, bone formation decreased, fracture delayed union, fracture malunion, fracture nonunion, low turnover osteopathy, pathological fracture, stress fracture, fracture, and femur fracture. *Id.* at ¶ 26. Dr. Madigan used "two industry-standard signal detection algorithms ... to assess whether or not Fosamax presented a safety signal" indicating oversuppression of bone turnover or AFFs. *Id.* at ¶ 25. The QScan pharmacovigilance software computed the statistics. *Id.* at ¶ 27. Dr. Madigan then compared the Fosamax signals to other oral bisphosphonates and a non-bisphosphonate used for the treatment and prevention of osteoporosis. *Id.* at ¶ 25. After reviewing the data, Dr. Madigan opined that

> industry standard pharmacovigilance techniques and datasources reveal the presence of a clear signal for oversuppression of bone turnover and associated atypical femur fracture events utilizing the terms selected by Merck for such analysis. By standard metrics of "signal" detection, the signal is strong, consistent, and not ambiguous. Of perhaps greater concern, the signal was striking in comparison to that for other drugs indicated for the prevention and treatment of osteoporosis. As early as 2001–2002, the

> spontaneous report data for Fosamax provide signals for a number of indicators of suppression of bone turnover. For the comparator drugs, such signals either never appear or appear years later.
>
> [*Id.* at ¶ 36.]

This opinion is admissible because it is based on a method that is sufficiently reliable. *See Jones*, 2010 WL 3311840, at *4. Two factors that a court may take into consideration in determining reliability is whether the methodology has been subjected to peer review and publication and whether there is general acceptance in the scientific community. *Daubert*, 509 U.S. at 593–94. Here, Dr. Madigan's method, data mining in pharmacovigilance, is generally accepted in the scientific community and has "become routine both in the pharmaceutical industry and amongst regulators worldwide." Madigan Report at ¶ 8. In fact, "[p]harmaceutical companies, health authorities, and drug monitoring centers use SRS databases for global screening for signals of new adverse events or changes in the frequency, character, or severity of existing adverse events (AEs) after regulatory authorization for use in clinical practice." *Id.* at ¶ 9. "SRS systems provide the primary data for day-to-day drug safety surveillance by regulators and manufacturers worldwide." *Id.* at ¶ 14. In addition, the QScan software Dr. Madigan used in formulating his opinion is generally accepted by the scientific community because it "has been in widespread use for over 10 years and has been validated extensively." *Id.* at ¶ 28. Moreover, "[m]any peer-reviewed publications report results derived from QScan." *Id.* Thus, Dr. Madigan's methodology is sufficiently reliable.

*9 Although Defendant argues that Dr. Madigan's methodology is unreliable because he did not review the substance of the adverse event reports to see if they actually involve AFFs or oversuppression of bone turnover, this argument is inappropriate on a *Daubert* motion. Dr. Madigan's testimony will be subject to cross-examination, and the credibility of his opinion will be ultimately determined through the adversarial process. Dr. Madigan's methodology is sufficiently reliable because it is generally accepted in the scientific community, and therefore, Plaintiffs have satisfied the second prong of *Daubert*.

**3. Dr. Madigan's Testimony Fits the Facts of the Case**

Lastly, Dr. Madigan's testimony fits the facts of the case and will assist the trier of fact because it is related to Plaintiffs' failure to warn claim. *See Jones*, 2010 WL 3311840, at *4. A failure to warn claim requires a plaintiff to show "(1) that a manufacturer has a duty to warn (2) against dangers resulting from foreseeable uses about which it knew or should have known and (3) that failure to do so was the proximate cause of the harm." *In re Fosamax Prods. Liab. Litig.*, 2013 WL 76140, *3 (S.D.N.Y. Jan.7, 2013). Dr. Madigan's testimony fits the facts of this case because he opines that "[a]s early as 2001–2002, the spontaneous report data for Fosamax provide[d] signals for a number of indicators of suppression of bone turnover," meaning Defendant knew or should have known that Fosamax caused certain dangers in 2001–2002, thus imposing on Defendant a duty to warn of those dangers. Madigan Report at ¶ 36.

Defendant, however, argues that Dr. Madigan's testimony does not fit the facts of the case because it is irrelevant since there is no reasonable standard of care that would have required Defendant to conduct data mining. This is also a matter best left to the credibility determination of the jury.

As a result, Dr. Madigan's expert testimony is admissible under *Daubert* because he is qualified, he used a sufficiently reliable methodology, and his opinion fits the facts of the case.

**D. Dr. Blume**

Dr. Blume is offered as an expert in pharmacovigilance and FDA regulation. Plaintiffs offer the testimony of Dr. Blume to: (1) "address the timeliness and completeness of the efforts undertaken by [Defendant] ... to fully inform prescribers and patients of the increasingly adverse benefit risk assessments associated with long-term Fosamax use in postmenopausal women"; (2) "evaluate the negative consequences of protracted bone oversuppression," including AFFs, in people receiving Fosamax; and (3) "to consider the pharmacovigilance activities undertaken by [Defendant] to evaluate the noted adverse events during the relevant time periods" [docket # 119, Ex. 33, Dr. Blume's Report ("Blume Report") at ¶ 6].

**1. Dr. Blume is Qualified as an Expert**

Dr. Blume received her Ph.D. in Pharmacology and Toxicology from the West Virginia University

Medical Center and is currently the President of Pharmaceutical Development Group, Inc. (PDG), "a consulting firm ... specializing in pharmaceutical development and registration activities." *Id.* at ¶ 1. In this role, she "has been responsible for preclinical and clinical (Phases I–IV) programs associated with pharmaceutical product development and the securing of pre-marketing approvals" for many drugs before the FDA. *Id.* at ¶ 2. Additionally, Dr. Blume has directed "all phases of interactions with [the] FDA relating to the prosecution of New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), Supplements to New Drug Applications (sNDAs), and the associated approval procedures," including "the collection and evaluation of postmarketing adverse medical events, the preparation of updated product labeling, and the dissemination of accurate, complete and timely product-related information to health care providers." *Id.* at ¶ 3. She was responsible for "regulatory review of promotional and education materials for both brand-name and generic drug products." *Id.* Dr. Blume's responsibilities include the "design, execution, and interpretation of pivotal safety-related trials and the development and implementation of pharmacovigilance procedures intended to detect new safety signals and track the evolution of previously identified signals." *Id.* at ¶ 4. She has directed "all phases of interactions with the FDA relating to post-approval labeling procedures regarding changes to safety-related information based upon postmarketing signal tracking and pharmacovigilance efforts," including "collection and evaluation of postmarketing adverse medical events, review and interpretation of the results of postmarketing clinical studies, the preparation of updated product labeling and other communication tools, and the dissemination of new product information to health care providers, patients, and consumers." *Id.* at ¶ 5. Dr. Blume possesses the knowledge, skills, and training necessary to qualify her as an expert. *See In re Paoli,* 35 F.3d at 741. Defendant does not dispute Dr. Blume's qualifications.

**2. Dr. Blume's Methodology Is Sufficiently Reliable**

***10** Dr. Blume reviewed published studies (Blume Report at ¶¶ 57–74), Merck's Period Safety Update Reports (*id.* at ¶ 75), Dr. Madigan's report (*id.* at ¶¶ 76–78), Merck's Worldwide Adverse Experience System ("WAES") (*id.* at ¶ 79), and epidemiological studies (*id.* at ¶¶ 82–90). *See also* docket # 119, Ex. 5, Dr. Blume's Deposition ("Blume Dep.") at 148:9–18; 338:9–20 (stating that she looked at the WAES database, literature reports, epidemiological studies, the AERS database, and Dr. Madigan's report). She discussed the "specific regulatory procedures and regulations" pharmaceutical manufacturers have to comply with, including procedures and regulations related to FDA approval, labeling, postmarketing surveillance, and reporting requirements. *Id.* at ¶¶ 11–34. Dr. Blume evaluated all of this information using "her years of experience" in "the industry," *see In re Viagra Products Liability Litigation,* 658 F.Supp.2d 950, 962 (D.Minn.2009), and opined that

> the scientific literature, Merck's internal adverse event database, the AERS database, and epidemiology analyses confirmed the increasingly adverse risk-benefit profile related to long-term Fosamax use in the indicated populations. However, Merck permitted their labeling and other prescriber information to remain static with respect to both the deteriorating risk-benefit assessment and the escalation in ... [AFF] reports. Such omissions do not comply with the regulatory and industry standards of responsible pharmaceutical companies .... Merck also should have undertaken timely and adequate studies to more clearly elucidate the risks of Fosamax use in the various indicated populations. Finally, Merck should have disseminated Dear Healthcare Professional Letters to advise prescribers and their patients of the escalating safety and efficacy concerns. Merck's omissions have likely resulted in the exposure of numerous patient populations to unnecessary risks associated with the initiation and ongoing treatment with Fosamax.
>
> [Blume Report at ¶ 110.]

Dr. Blume states that "[b]y the early 2000's, it was known that ... [AFFs] were clinically significant events ...." *Id.* at ¶ 109. Dr. Blume opines that Defendant should have changed the Fosamax label "to include escalating warning and precautionary risk information related to" AFFs. *Id.* Instead, Dr. Blume notes that Defendant "did not identify these fractures in the labeling until 2009" even though it received reports that AFFs were "associated with Fosamax use as early as 2002." *Id.* at ¶¶ 31, 82.

Defendant argues that the Court should exclude Dr. Blume's opinions on: (1) the legal requirements governing pharmaceutical manufacturers and Defendant's compliance with those requirements; (2) Defendant waiting too long to add information about femur fractures

to the Adverse Reactions section of the label; (3) Defendant failing to add a warning or precaution about femur fractures to the Fosamax label before 2009; (4) Defendant's failure to timely investigate a potential link between Fosamax and AFF; (5) Defendant's alleged motives or state of mind; (6) the causation or mechanism of AFF; and (7) the drug Evista is safer than Fosamax. Yet, because *Daubert* concerns the narrow issue of whether expert testimony is admissible, this is not the appropriate time for Defendant to request that the Court preclude Dr. Blume from testifying about certain topics. Defendant may question Dr. Blume's opinions or methodology on cross-examination. *See Milward*, 639 F.3d at 15 (stating "[s]o long as an expert's scientific testimony rests upon "good grounds," based on what is known, ..., it should be tested by the adversarial process, rather than excluded").

***11** Despite Defendant's issues with Dr. Blume's opinions, Plaintiffs have satisfied the second prong of *Daubert* because Dr. Blume's methodology is sufficiently reliable.

**3. Dr. Blume's Testimony Fits the Facts of the Case**

Dr. Blume's testimony fits the facts of the case because she opines that it was known in the early 2000's that AFFs were associated with Fosamax use. *See* Blume Report at ¶¶ 31, 82. Dr. Blume's testimony is relevant and will assist the trier of fact in deciding Plaintiffs' failure to warn claim because Dr. Blume's opinion is relevant to whether and when Defendant knew or should have known that AFFs were associated with Fosamax and therefore, when Defendant should have sought a label change. *See Schneider*, 320 F.3d at 404 (recognizing that expert testimony must "be relevant for the purposes of the case and must assist the trier of fact").

**E. Treating Physicians**

Defendant argues that the Court should preclude causation testimony from Plaintiffs' treating physicians —Drs. Busch, Lindsay, Fletcher, and Limes—because: (1) Plaintiffs have not provided Rule 26 disclosures for any of the treating physicians; and (2) none of the treating physicians are able to offer a reliable causation opinion to a reasonable degree of medical certainty. Plaintiffs, however, assert that they do not intend to elicit expert testimony from the treating physicians; instead, the treating physicians will testify about Mrs. Glynn's care and treatment, which does not require Rule 26 disclosures.

Treating "physicians are not required to submit expert reports when testifying based on their examination, diagnosis and treatment of a patient." *Patterson v. Howard*, 2010 WL 1050052, *4 (D.N.J. Mar.18, 2010). Federal Rule of Civil Procedure 26(a)(2)(B) requires a witness to submit a written report only "if the witness is one retained or specially employed to provide expert testimony in the case or one whose duties as the party's employee regularly involve giving expert testimony." A "treating physician is not necessarily retained or specially employed to provide expert testimony simply because he or she proffers on causation and prognosis" because "doctors may need to determine the cause of an injury in order to treat it." *Pease v. Lycoming Engines*, 2012 WL 162551, *12 (M.D.Pa. Jan.19, 2012). In order to "determine whether a party retained or specially employed a treating physician to provide expert testimony," the Court must examine "whether the treating physician acquired his opinion as to the cause of ... plaintiff's injuries directly through his treatment of the plaintiff." *Id.* (internal quotation omitted). As a result, treating physicians are not required to submit expert reports "if they form their opinion on causation or prognosis as part of the ordinary care of a patient." *Id.*

Therefore, the testimony of Drs. Busch, Lindsay, Fletcher, and Limes is appropriate if it is based on their care and treatment of Mrs. Glynn. This Court will not allow, however, any expert testimony on causation from these physicians.

**II. CONCLUSION**

***12** For the reasons outlined above, this Court denies Defendant's *Daubert* Motion as to Drs. Cornell, Klein, Madigan, and Blume. An appropriate Order accompanies this Opinion.

**All Citations**

Not Reported in F.Supp.2d, 2013 WL 1558690, 91 Fed. R. Evid. Serv. 106

Footnotes

1 The abbreviation of atypical femur fracture (singular) is "AFF."

2 Db13 means page 13 of Defendant's brief.

3 Pharmacovigilance is the surveillance of spontaneous reporting system ("SRS") databases "for the early detection of drug hazards that are novel by virtue of their clinical nature, severity, and/or frequency." *Id.* at ¶ 7.

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# EXHIBIT 8

2011 WL 13576
Only the Westlaw citation is currently available.
United States District Court,
E.D. Pennsylvania.

In re AVANDIA MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION.
This Document Relates to All Actions.

Avandia MDL No. 1871.
|
No. 2007–MD–1871.
|
Jan. 4, 2011.

***ORDER***

CYNTHIA M. RUFE, District Judge.

***1 AND NOW,** on this 3rd day of January, 2011, upon consideration of GlaxoSmithKlines's Motions to Exclude the Testimony of Plaintiff Steering Committee Expert Witnesses Eliot A. Brinton, M.D. [Doc. No. 734], Nicholas P. Jewell, Ph.D. [Doc. No. 736] and Allan D. Sniderman, M.D. [Doc. No. 740], and for the reasons set forth in the attached memorandum opinion, it is hereby **ORDERED** that Defendant's Motions are **DENIED.**

It is so **ORDERED.**

***MEMORANDUM OPINION AND ORDER***

Presently before the Court are GlaxoSmithKline LLC's (GSK's) Motions to Exclude the Testimony of Plaintiff Steering Committee's Expert Witnesses Eliot A. Brinton, M.D.,[1] Nicholas P. Jewell, Ph .D.,[2] and Allan D. Sniderman, M.D.,[3] Plaintiffs' responses thereto, and GSK's replies. The Court has reviewed each expert's report and held a *Daubert* hearing to hear argument and testimony regarding the admissibility of the expert testimony on September 20–22, 2010. For the reasons set forth below, the Court will deny the motions to exclude the testimony of Drs. Brinton, Sniderman, and Jewell.

***Factual Background***

Plaintiff intends to offer Drs. Brinton, Jewell and Sniderman, among other experts, as generic expert witnesses for civil actions in MDL No. 1871. Their testimony will cover the alleged health risks involved in taking the drug Avandia, which is manufactured by GSK. GSK challenges the admissibility of this evidence, asserting that the experts used unreliable methods to reach their conclusions that Avandia may cause myocardial infarction in diabetic patients taking it to control their blood sugar.

***Standard of Review***

Federal Rule of Evidence 702 reads:

> [I]f scientific, technical or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient fact or data, (2) the testimony is the product of reliable principles and methods; and (3) the witness has applied the principles and methods reliably to the facts.

The Third Circuit has distilled this rule to two essential inquiries: 1) is the proffered expert qualified to express an expert opinion; and 2) is the expert opinion reliable?[4] In this case, GSK primarily challenges the reliability of the opinions.

Under the Third Circuit framework, the focus of the Court's inquiry must be on the experts' methods, not their conclusions. Therefore, the fact that Plaintiffs' experts and defendants' experts reach different conclusions does not factor into the Court's assessment of the reliability of their methods.[5] The experts must use good grounds to reach their conclusions, but not necessarily the best grounds or unflawed methods.[6]

Here, the scientific question the experts are addressing is whether there is a reasonable degree of scientific certainty that Avandia can cause myocardial infarctions. To meet

the *Daubert* standard, the experts must demonstrate that they have good grounds for their causation opinion (i.e. the opinion is based on methods and procedures of science, not subjective belief) and a reasonable degree of scientific certainty regarding their causation opinion. [7]

*2 Expert evidence must be relevant and reliable to be admissible. The Court must consider: 1) whether the expert's theory can be tested; 2) whether studies have been subject to peer review and publication; 3) the potential for error in a technique used; and 4) the degree to which a technique or theory (but not necessarily a conclusion) is generally accepted in the scientific community. [8] In cases such as this one, where the allegation is that a chemical (Avandia) causes a medical condition (myocardial infarction) experts should rely primarily on epidemiological studies to test their theory that the drug causes the disease. Double-blind randomized control trials, and particularly monotherapy trials comparing Avandia use to a placebo, are the "gold standard" of epidemiology. The best studies are designed and powered to test the outcome of interest (e.g., in this case, the most telling trial would be designed and have adequate subjects needed to study the impact of Avandia on the heart, not its effectiveness in managing blood sugar or other outcomes). [9]

***Discussion***

**1. General Issues**

*Epidemiological Methods*

The research on safety risks from Avandia use falls into three categories: 1) randomized control trials ("RCTs"), such as RECORD, DREAM, and ADOPT; 2) meta-analyses, such as NISSEN, SINGH, and MANUCCI; 3) and observational studies (such as the Harvard and Michigan studies). [10]

GSK argues that randomized control trials are the "gold standard" for epidemiological research, and that Plaintiffs' experts can find no support for their position in the RCTs conducted because the association between Avandia and myocardial infarction did not reach statistical significance in any of the RCTs. Therefore, GSK argues, the experts cannot rule out the possibility that the association was due to chance alone. In addition, GSK argues, none of the RCTs found Avandia to be associated with a statistically significant increase in atherosclerosis, which Plaintiffs' experts agree is the principal cause of myocardial infarction.

GSK also argues that Plaintiffs' experts do not give adequate weight to the findings of the RECORD study, which was a large RCT designed and carried out by GSK specifically to compare the cardiovascular safety of Avandia to that of Actos (a competitor medication in the same class). The RECORD study found no statistically significant increase in myocardial infarction, cardiovascular hospitalization or death.

Similarly, GSK argues that Plaintiffs improperly disregard the findings of the ADOPT and DREAM trials. Both are RCTs designed to test to the efficacy of Avandia for glycemic control, not its safety, and in both the association between Avandia and myocardial events approached but did not reach statistical significance.

Plaintiffs' experts each made specific criticisms about the RCT study designs and pointed out issues which complicate interpretation of the data, such as concurrent use of statins and a high drop out rate. These will be discussed in detail below. The experts also explained that when both the treatment group and the control group have a high background risk of myocardial infarction by reason of being diabetic, a large number of subjects is needed to adequately test whether Avandia is associated with an increased risk of myocardial infarction. If the sample size is too small to adequately assess whether the substance is associated with the outcome of interest, statisticians say that the study lacks the *power* necessary to test the hypothesis. Plaintiffs' experts argue, among other points, that the RCTs upon which GSK relies are all underpowered to study cardiac risks.

*3 To overcome the problem of underpowered studies, researchers may combine data from several studies into a meta-analysis. The NISSEN meta-analysis combined 42 clinical trials, including the RECORD trial and other RCTs, and found that Avandia increased the risk of myocardial infarction by 43%, a statistically significant result ($p = .031$). Plaintiffs point out that all the data used by Dr. Nissen in his meta-analysis came from GSK's own clinical trial registry. The NISSEN study was peer reviewed and published in the New England Journal of Medicine. Although GSK criticizes Plaintiffs' experts for relying on the NISSEN study, and notes that

meta-analysis generally can be unreliable, GSK points out no specific flaws or limitations in the design or implementation of the NISSEN meta-analysis, and the NISSEN results have been replicated by other researchers. For example, the SINGH meta-analysis pooled data from four long-term clinical trials, and also found a statistically significant increase in the risk of myocardial infarction for patients taking Avandia. [11] GSK and the FDA have also replicated the results of NISSEN through their own meta-analyses.

GSK argues that Plaintiffs' experts place too much reliance on meta-analysis (and particularly the NISSEN and SINGH studies), as meta-analysis is better for generating hypotheses than for testing them. While this may be true, the Court notes that if a statistically significant finding in a meta-analysis generates a hypothesis that Avandia is associated with a significant risk of heart attack, it may then become unethical to proceed with RCT of that substance, especially given the number of test subjects which would be required to adequately power a RCT to study whether Avandia causes heart attacks. Therefore, in some cases the science must proceed based upon less rigorous methods. This does not mean that inferences about causation cannot be made; it simply means that the expert must more carefully examine possible sources of bias or confounding and other factors which may make the study a weak indicator of causation.

Additionally, GSK argues that Plaintiffs' experts rely too heavily on observational studies, in which patients are not randomly assigned to treatment groups, and hence the patients for whom Avandia is prescribed may be different in some important ways from those in the control group who take another drug or no drug. One must carefully consider sources of bias, confounding, and alternative mechanisms.

*Making Conclusions about Causation and the Bradford–Hill Criteria*

Bradford–Hill criteria are used to assess whether an established association between two variables actually reflects a causal relationship. [12] Because these criteria are so well established in epidemiological research, it appears that the experts often consider these factors without citation to Bradford–Hill. When making causal inferences from associations between exposure to a chemical or drug and a disease outcome, the relevant Bradford–Hill criteria are: temporal relationship between the exposure and the outcome; the strength of the association between the exposure and the outcome; the dose-response relationship; replication of findings; the biological plausibility of or mechanism for such an association; alternative explanations for the association; the specificity of the association; and the consistency with other scientific knowledge. An expert need not consider or satisfy every criteria in order to support a causal inference. GSK argues that the Plaintiffs' experts equate association with causation and fail to apply the Bradford–Hill criteria when making causal inferences. The Court will examine this assertion in detail in the sections that follow.

**4 Although GSK asserts that a plausible biological mechanism to explain any association is one of the weaker Bradford–Hill criteria, GSK goes on to argue that Plaintiffs' experts lack a reliable theory for and proof of a biological mechanism of action. Specifically, they argue that the research on Avandia does not show that it causes a progression of atherosclerosis, the primary mechanism for myocardial infarction. [13]

As discussed in detail below, the Court finds that Plaintiffs' experts used reliable methods to find an association between Avandia and myocardial infarction, and adequately explored the Bradford–Hill criteria before drawing causal conclusions from that association

*Study Selection*

GSK argues that Plaintiffs' experts selectively reviewed studies which supported their causal inferences, and ignored studies which found no association between Avandia and adverse cardiac events. GSK argues that Plaintiffs' experts need to give detailed explanations regarding their decisions to rely on some studies and dismiss the importance of others. For example, the experts rely heavily upon the NISSEN and SINGH meta-analyses, but reject the MANNUCCI meta-analysis which found no correlation between Avandia usage and myocardial infarction. Of the twenty-three published observational studies, nine found a statistically significant increase in myocardial infarction for Avandia users, thirteen found no statistically significant correlation, and one showed a statistically significant protective effect. GSK argues that Plaintiffs' experts need to justify their reliance on the studies supporting their causal inference and rejection of the studies which are not supportive.

As the Court will discuss below, each of Plaintiff's experts adequately justified their reliance on some studies and rejection of others using scientific and statistical principles.

*Statistical Significance*

GSK criticizes Plaintiffs' experts for utilizing a clinical rather than a scientific standard of proof. Under a clinical standard, a doctor makes a risk-benefit analysis, whereas under a scientific standard one must have statistically significant findings to justify a causal inference. GSK also notes that Plaintiffs' experts rely on RCTs in which the positive correlation between Avandia and myocardial infarction does not reach statistical significance, such as DREAM, and ADOPT. Because the results are not statistically significant, the increased occurrence of myocardial infarction in the group taking Avandia may simply be due to chance. GSK argues that findings which are not statistically significant, although arguably *clinically useful*, are not *scientifically reliable*, and therefore do not meet the *Daubert* standard. In this case, while it is true that the experts point to the trend indicating increased risk found in many studies, only some of which reach statistical significance, the experts use the non-significant data only to bolster their inferences and not as their sole source of support. Therefore, the Court finds that the experts have sufficient statistically significant data to support their causal inferences, in combination with additional analysis.

*The FDA*

***5** Finally, GSK argues that the FDA has convened two advisory committee ("Ad Com") meetings regarding Avandia, in 2007 and 2010, and has opted not to vote on the question of whether Avandia *causes* myocardial infarction. Instead, the FDA has only stated that it has significant safety concerns about ischemic cardiac events for Avandia users. In 2007, the FDA Ad Com overwhelmingly voted "yes" when asked whether the available data supports the conclusion that Avandia increases cardiac ischemic risk in patients with Type II diabetes mellitus. After that Ad Com meeting, the FDA asked GSK to conduct a study comparing cardiovascular outcomes for Avandia versus Actos (the TIDE study). The FDA later suspended that study due to safety concerns about the risks associated with Avandia. Plaintiffs note that the Ad Com experts were not reassured by evidence presented to exonerate the drug in 2010, and the FDA took regulatory action to mitigate risk by significantly limiting the use of Avandia in the United States. The FDA's European counterpart suspended sales completely. Although the Court finds that the FDA did not vote on the precise question at issue here, that finding is not dispositive of the question as to whether Plaintiffs' experts meet the *Daubert* standard.

*Defining Adverse Events*

Finally, GSK argues that some of Plaintiffs' experts define "adverse event" too broadly, including myocardial ischemic events as well as myocardial infarctions. Plaintiffs' experts counter that myocardial ischemic events occur when there is a lack of oxygen to the heart muscle, and prolonged oxygen deprivation is the cause of myocardial infarction. Therefore, the difference between the two is a matter of degree; they are not caused by different mechanisms. In addition, Plaintiffs are forced, to some extent, to rely upon evidence regarding the broader category of myocardial ischemic events by the design of the studies (including those conducted by GSK) which broadly defined the outcomes of interest. However, by virtue of their expertise and the available data, the Court finds that the experts were able to draw reliable conclusions about myocardial infarction.

**2. Expert Specific Issues**

*Eliot A. Brinton, M.D.*

Dr. Brinton is a diabetologist and lipidologist, trained in endocrinology. He is primarily a clinical researcher and professor, employed by the University of Utah School of Medicine, but he also maintains a clinical practice. He once served on the Avandia Speakers' Bureau for GSK, but over time he became concerned with the lipid effects of Avandia, which were adverse compared to a similar drug (Actos), and eventually reached the conclusion that Avandia has the potential to cause cardiovascular disease. He continues to serve as a national advisor and speaker for GSK with regard to their lipid drug Lovaza, and has applied for grants from GSK to conduct research on Lovaza, but will no longer advocate for the use of Avandia based on his conclusions about the dangers of the drug.

***6** When Actos and Avandia were initially approved, Dr. Brinton stated that he had no preference for one over the other. Later he became aware that there were differences in lipid effects, and began to prescribe Actos significantly

more often in his practice.[14] The change in his use of Avandia was based not only on his clinical observations, but also on his review of the scientific research. Even before the NISSEN study was published, Dr. Brinton had reviewed the ADOPT and DREAM studies, which found cardiovascular detriment from Avandia use (albeit not a statistically significant detriment), and the PROactive study, which found cardiovascular benefits. After reading these studies, he had nearly stopped prescribing Avandia. Once the NISSEN study was published, he was puzzled by the FDA's decision to keep Avandia on the market, given that it had no meaningful advantage over Actos and was correlated with an increase in cardiovascular problems.[15]

Dr. Brinton's report focuses both on the adverse impact of Avandia on lipoprotein metabolism (a biological mechanism for ischemic heart disease, including myocardial infarction), and on the direct evidence that use of Avandia increases myocardial ischemic events.

*Mechanism of Action*

According to Dr. Brinton's report, one way that Avandia may cause myocardial infarction is by its effect on low-density lipoprotein (LDL) and apo B. While apo B levels are the strongest single predictor of atherosclerosis risk, 90% of apo B molecules are found contained in LDL particles, hence LDL (including LDL–P and LDL–C levels) is also often used to predict risk.[16] Another excellent predictor of risk is non-HDL cholesterol.[17] The standard predictor of cardiovascular disease risk is LDL–C.[18] Avandia studies report increases in LDL–C levels, generally in the 15–20% range on average, with some individuals showing even larger increases.[19] As statins are often prescribed for patients taking Avandia, the true effect of Avandia is probably underestimated in the research.[20]

Plasma apo B levels are increased in a dose-dependent manner by Avandia, by about 10% on average in studies not conducted by GSK.[21] LDL–P levels are also increased by Avandia usage. One published double-blind randomized control trial (DBRCT) found an 8% increase in LDL–P for patients taking Avandia (compared to a 4% *decrease* with Actos).[22] Non–HDL–C is increased by 20% or more with Avandia usage. Dr. Brinton rejects GSK's argument that Avandia's impact on LDL particle size is a mitigating factor, concluding that all three particles negatively effected are atherogenic, so even if Avandia does increase LDL particle size (a mitigating factor), the net effect of Avandia on lipids is negative.[23] He also evaluates GSK's arguments that the particle ratios are more important than the increase in negative particles, and that the approximately 5% increase of High–Density Lipoproteins (HDL) with Avandia usage is beneficial.[24] Dr. Brinton points out that there is no clearly established correlation between changes in the complex family of HDL molecules and a reduction in atherosclerosis and adverse events.[25] For example, Avandia decreases plasma apo A–1 levels, and it is those molecules, not the HDL itself, that appear to be responsible for the beneficial effect of HDL on atherosclerosis.[26] Avandia also reduces HDL–P.[27] Overall, Dr. Brinton notes, GSK simply does not have research findings to back its assertion that Avandia is linked to a favorable increase in HDL levels.[28] Furthermore, research on HDL-raising therapies reveals that some increases in HDL increase rather than decrease adverse cardiovascular events.[29]

*7 Similarly, Dr. Brinton talks about triglycerides (TC) as a mechanism by which Avandia increases the risk of cardiovascular disease, acknowledging that the mechanism for this relationship between triglycerides and atherosclerosis are not well understood.[30] Again, Dr. Brinton addresses GSK's arguments regarding this biological mechanism.[31]

Dr. Brinton discusses how Avandia usage increases levels of LpPLA2, which increase then destabilizes atherosclerotic plaques. The plaques are then vulnerable to rupture, causing myocardial infarctions.[32] LpPLA2 was discovered by GSK scientists, who are well aware of its role in coronary disease, but declined to study the impact of Avandia on LpPLA2 and to publish early studies which found Avandia increased LpPLA2.[33] Dr. Brinton evaluates GSK's position regarding LpPLA2, and gives detailed, research-based reasons for his disagreement.

Finally, Dr. Brinton discusses a well established connection between Avandia use and congestive heart failure (CHF).[34] The RECORD study revealed ten deaths from CHF in the Avandia group, and only two

in the control group. Dr. Brinton notes that CHF can contribute to myocardial ischemia. CHF impairs arterial blood flow, and can increase the likelihood and severity of ischemia to an area served by an atherosclerotic artery.[35] The combination of Avandia and insulin (a commonly prescribed, though off-label, combination) or Avandia and nitrates leads to an additive problem with CHF and is associated with increased myocardial ischemic events .[36]

Dr. Brinton also spends many pages in his report explaining why GSK's assertions of unchanged or reduced atherosclerosis with Avandia usage are somewhat misleading. For example, many patients taking Avandia are put on statins for associated increases in LDL–C.[37] Because statins are known to reduce atherosclerosis and cardiovascular disease events by about 30%, researchers may not see the true effects of Avandia usage on atherosclerosis.[38] In addition, some studies were underpowered to find effects on atherosclerosis (e.g., APPROACH).[39]

*The Research Supporting an Inference of Causation*

Dr. Brinton discusses which studies are best designed for reaching causal conclusions about Avandia's impact on the heart. He notes that the comparator treatment in a research study is an important consideration.[40] The impact of Avandia is clearest if the comparison group gets no treatment or a placebo. However, this scenario is not clinically relevant, as doctors rarely decide between prescribing Avandia and no treatment.[41] Therefore, direct comparison of Avandia to other glycemic control treatments is more clinically relevant, and most studies were designed to compare Avandia to other active drugs.

Dr. Brinton acknowledges that some clinical trials and observational data suggest that Avandia does not cause harm, but feels that the preponderance of data shows that it does increase cardiovascular disease events. He examines three types of evidence, beginning with RCTs and especially double-blind RCTs designed and powered to study cardiovascular effects. However, he notes again that even in a double-blind RCT, doctors may, and often do, prescribe statins to their patients in addition to Avandia or the control medication. The disproportionate use of statins in the Avandia arm of a trials can distort the rate of cardiac events in Avandia's favor.[42] Another disadvantage of using a DBRCT is that, because of the cost and complexity of conducting them, they are often inadequate in size to truly address the risk of serious but uncommon outcomes. Dr. Brinton also points out that many large RCT, such as ACCORD, ADVANCE, BARI–2D, and VADT, randomly assigned patients to a *treatment strategy* (intensive versus standard) but assignment to Avandia or another medication was not randomized. Therefore, to the extent that the researchers make findings as to the safety profile of Avandia from these studies, they should be considered observational studies and not the gold standard RCTs.

***8** Dr. Brinton discusses the RECORD trial (a RCT, but not a double-blind study) at length, and criticizes the lack of specificity in the endpoints of interest (for example, categorizing all deaths of unknown cause as cardiovascular deaths, for both the treatment and control arms of the study). He also notes that the prescribing doctors were permitted to measure patients' lipid profiles and even encouraged to prescribe statins. Statin use increased 9% more in the Avandia arm than the control arm. While this is clinically appropriate, it creates a serious problem in interpreting the study. Statin use (in both the treatment and control groups) also led to a lower-than-expected rate of cardiovascular disease overall in the study, which means that the study lacked statistical power. This problem with statistical power was compounded by the fact that a large percentage of study participants (in both arms) dropped out of the study.

Dr. Brinton gives a similarly detailed, scientific critique of the APPROACH, ADOPT, and DREAM studiesall studies with outcomes contrary to his opinion. He does not simply ignore these studies, as GSK suggests, but instead analyzes their strengths and weaknesses before concluding that they neither contradict nor undermine his opinion.

Next, Dr. Brinton turns his attention to meta-analyses of RCTs. A meta-analysis statistically combines studies, thereby increasing the statistical power so that researchers can study an infrequently occurring outcome of interest. Dr. Brinton points out two potential drawbacks of meta-analysis: 1) biased selection of studies; and 2) the results of one large trial can skew the overall findings. In 2007, the New England Journal of Medicine published the NISSEN meta-analysis, which combined results from 42 double-blind RCTs and found that patients taking Avandia had a statistically significant 43% increase in

myocardial ischemic events. NISSEN used *all* publicly available data from double-blind RCTs of Avandia in which cardiovascular disease events were recorded, thereby eliminating one major drawback of meta-analysis: the biased selection of studies. The SINGH, GSK and FDA meta-analyses replicated the key findings of the NISSEN study.[43] Meta-analyses combining studies which compared Avandia to a placebo, as opposed to an alternative treatment, showed a statistically significant 60% increase in myocardial ischemic events.

Dr. Brinton also points to the potential drawbacks of observational studies, including confounding and bias. These disadvantages, he notes, can be reduced by careful study design and execution. The advantage is that a much larger number of subjects can be studied using the observational method. Dr. Brinton reviewed twelve major observational studies, ten of which show statistically significant or nearly significant increases in major cardiovascular disease events for patients taking Avandia compared to the control groups. He cites to the strong evidence found in the Brownstein and Lipscombe studies, and discusses the limitations of the studies which did not find an association between Avandia and heart disease. One was cross-sectional, rather than longitudinal, in design and did not collect data which would allow researchers to control for socio-economic status, co-morbid conditions, existing health status, medical history, medication dose, and time on the drug.[44] The second, by Margolis, had a very wide confidence interval.[45]

***9** Dr. Brinton points out that the research (both meta-analytical and observational) shows that a significant increase in myocardial infarction and death occurs during the first six months of Avandia treatment when compared to other treatments.[46] He believes this supports his view that Avandia is an independent, causal factor.

GSK points out that Dr. Brinton did not take the position that Avandia causes heart attack until he was retained as an expert in this litigation. In fact, in 2007, Dr. Brinton recommended to the Utah State Medicaid Pharmaceutical and Therapeutics Committee that they keep both Actos and Avandia on their formulary, despite his observations about Avandia's negative impact on lipid profiles.[47] GSK argues that his current opinion is not reliable because it has changed since 2007. The Court finds that this criticism of Dr. Brinton goes to his credibility, and not to his methods. While a jury might find Dr. Brinton less credible because of his past position on Avandia, the opinions expressed in this case are based on reliable scientific methodology (the review of peer-reviewed, published studies and data using well established statistical and scientific principles).

GSK also argues that Dr. Brinton departed from scientific methodology by relying on data that is not statistically significant .[48] Although he did cite to studies in which the results were not statistically significant, his conclusions did not rest on those studies alone; rather, they were used to bolster the conclusions he drew from studies in which the findings were statistically significant. Similarly, the Court finds that Dr. Brinton found scientific evidence of an association, which he examined to rule out the effects of chance, bias and confounding, and then applied the Bradford–Hill criteria to reach a causal conclusion. GSK states that a biologically plausible mechanism is one of the weakest of the Bradford–Hill criteria, yet argues that the proven effects of Avandia on certain biomarkers does not necessarily translate into cardiovascular harm as Dr. Brinton hypothesizes. Because the Court finds that Dr. Brinton's hypotheses about plausible mechanisms are based on scientific data about both the links between Avandia and lipid profiles and the connections between lipid profiles and outcomes, and as one of several Bradford–Hill criteria (including consistency of findings, strength of association, dose response, temporal association), the Court does not find his analysis unreliable under *Daubert*.

Overall, the Court does not find that Dr. Brinton's conclusions were arrived at by "litigation-driven methodology" nor by his own clinical impressions, but rather by a thorough review and analysis of the published literature. When he rejects research that does not support his opinion, he explains why he finds that research flawed and not compelling. That is, his approach to the data was scientifically reliable. Any inconsistency in Dr. Brinton's opinions over time, and any flaws in his conclusions, go to weight, not admissibility.

*Allan D. Sniderman, M.D.*

***10** Dr. Sniderman is a cardiologist, medical researcher, and professor at McGill University. His research focuses on lipoprotein metabolism and, in particular, on the importance of apoB as a marker for vascular

disease. His work has been published in over 280 peer-reviewed publications. He believes that Avandia significantly increases myocardial ischemic events, including myocardial infarctions, and that the adverse changes it causes to apoB underlie a causal relationship. GSK does not challenge Dr. Sniderman's qualifications as a cardiologist, but does challenge his ability to analyze and draw conclusions from epidemiological research, since he is not an epidemiologist. GSK's briefs do not elaborate on this challenge, and in any event the Court finds it unconvincing given Dr. Sniderman's credentials as a researcher and published author, as well as clinician, and his ability to analyze the epidemiological research, as demonstrated in his report.

Dr. Sniderman begins by noting the undisputed claim that Avandia causes congestive heart failure through fluid retention. Once a heart begins to fail, even with therapy it can result in progressive deterioration. [49] When a medication like Avandia also increases LDL cholesterol and apo-B, [50] it may cause clinical events, including myocardial infarction. [51]

The reasoning behind Dr. Sniderman's causal conclusions rests upon his research on, and understanding of, the action of apoB lipoproteins. ApoB particles carry cholesterol and triglycerides from the liver and intestines to the rest of the body, and, according to Dr. Sniderman, provide a more accurate measure of the number of LDL particles in the system, and of cardiovascular risk, than measures of LDL cholesterol. [52] He cites to both epidemiological studies and research on the effect of statins to support his opinion that apoB is a better predictor of cardiovascular risk than LDL cholesterol. [53] He notes that in patients with Type 2 diabetes, LDL cholesterol is not generally elevated, but apoB is. [54] Therefore, in diabetics in particular, apoB is the best predictor of cardiac risk.

It is well documented by GSK's own research that Avandia use produces a statistically significant increase in LDL. [55] About one-third of patients studied experienced a substantial increase in LDL cholesterol, and another third a marked increase. [56] About one-third of patients studied experienced no increase in LDL cholesterol, but in some of those patients, apoB may increase even where overall LDL cholesterol levels are stable. [57] In these patients, apoB is a better indicator of increased risk.

According to Dr. Sniderman, researchers (including himself) have established that apoB particles gradually *cause* atherosclerosis (this process may occur over decades), and that atherosclerosis then can *cause* cardiovascular death. He asserts that this is not a theory about increased risk, but an established scientific fact. [58] GSK disputes this conclusion, but points only to dated sources for its position that authorities do not recognize apoB as a better predictor than LDL of cardiovascular disease. [59] GSK acknowledges that a causal role for LDL cholesterol in cardiovascular disease has been established and corroborated by controlled clinical trials. [60] And LDL is clearly raised in the majority of patients taking Avandia.

***11** GSK argues that increases in HDL with Avandia use mitigate any increase in LDL or apoB. Dr. Sniderman responds by noting that the mechanisms by which HDL decreases risk are not well understood, and medication-induced increases in HDL do not necessarily translate into clinical benefits. [61] He also notes that increases in HDL were not found in all Avandia studies, and some studies found no change or even a decrease in HDL with Avandia use. [62] In addition, he notes that previous research has not reported whether the same individuals who experience increased LDL also experience increased HDL with Avandia use, thus achieving or maintaining a health ratio. [63] Looking at patient level data obtained from GSK, Dr. Sniderman found changes in LDL and HDL cholesterol were frequently dissociated.

In reviewing the evidence that Avandia causes myocardial infarction, Dr. Sniderman is cognizant of the methodological limitations of various studies, including: careful and specific documentation of adverse outcomes, the use of low-risk subjects, and the use of statins in concert with Avandia and the control medications. Because these factors led to a small number of adverse events being recorded in either the treatment or the control arm of the study, most RCTs were underpowered to detect, at statistically significant levels, the relationship between Avandia and adverse cardiac outcomes.

It is for this reason that those with concerns about Avandia's impact on the heart (including GSK and the FDA) turned to meta-analysis, which combines RCTs to increase the power of the statistical analysis. Although there are problems inherent in using meta-analysis, independent researchers, GSK, and the FDA have all replicated the findings of the NISSEN study, which found a statistically significant increase in myocardial infarction for patients using Avandia. The consistency of the findings lends credence to the results. [64] Dr. Sniderman points to the SINGH study, which combined the very trials GSK relies upon to show that Avandia is safe (RECORD, DREAM, ADOPT, DARGIE) and found a statistically significant increase in the risk of myocardial infarction for Avandia users.

GSK criticizes Dr. Sniderman and other experts for selectively discussing meta-analysis which support their position, and ignoring studies like MANUCCI which do not find increased risk. But Dr. Sniderman describes and critiques the MANUCCI study in his report. [65] He notes that some of the studies were of very short duration: the meta-analysis included studies as short as 4 weeks in duration, which is a reasonable amount of time to study a medication's effectiveness, but not its risks. [66] It also is unknown how statin use was distributed between the experimental and control arms of the studies. [67] For these reasons and others, Dr. Sniderman rejects the results of the MANUCCI study.

Observational studies further confirm the finding that Avandia is associated with an increased risk of myocardial infarction and mortality. [68] Dr. Sniderman asserts that although these studies are subject to confounding and bias, the consistency of the findings across studies and the effect size is telling. [69]

***12** Finally, Dr. Sniderman turns to the RCTs. RECORD, DREAM, and ADOPT were designed and conducted by GSK. Although RCTs are generally considered the "gold standard" of research studies, they may still have methodological flaws. Dr. Sniderman opines that RECORD is *not* strong evidence that Avandia does not increase the risk of ischemic disease, because of: 1) a low event rate in both arms of the study; 2) the high dropout rate; 3) the failure to design and/ or power the study to assess the risk of myocardial ischemia; and 4) the confounding effect of concurrent statin treatment, which was not controlled by investigators (use of statins in the Avandia arm exceeded use in the control arm by 9%). [70] Even with the differential use of statins, the RECORD study showed a trend of increased cardiovascular events for those in the Avandia arm of the study. [71]

The DREAM and ADOPT studies were designed to study the impact of Avandia on pre-diabetics and newly diagnosed diabetics. Even in these relatively low-risk groups, there was a trend towards an adverse outcome for Avandia users (e.g., in DREAM, the p-value was .08, which means that there is a 92% likelihood that the difference between the two groups was not the result of mere chance). [72] It is not clear whether statin use was allowed in the DREAM study. The ADOPT study was marred by a very high dropout rate (more than 40% of the subjects did not complete the four year follow up) and the use of statins during the trial.

The Court finds that Dr. Sniderman examined studies which both supported and contradicted his conclusions in arriving at his opinions, he used findings which were not statistically significant only to bolster his opinion based on statistically significant findings, he properly considered the relationship between myocardial ischemic events and myocardial infarction, he evaluated the potential for bias and confounding, and he engaged in a Bradford–Hill analysis, with particular attention to biological mechanisms, strength and consistency of findings, and temporal issues. The Court further finds that Dr. Sniderman considered Avandia's effect on both apoB and LDL, as well as other aspects of cardiac health. Accordingly, the Court will deny GSK's Motion to Exclude his testimony, because the Court finds his opinion to be scientifically reliable.

*Nicholas P. Jewell, Ph.D.*

Dr. Jewell has a Ph.D. in mathematics from the University of Edinburgh, Scotland, and is an expert in biostatistics. He has been a professor of biostatistics at the University of California, Berkeley for the past 28 years. He authored a well-reviewed textbook entitled *Statistics for Epidemiology*, as well as over 100 peer reviewed papers on biostatistics. He has served as an expert in other cases, including cases regarding the adverse cardiovascular effects of Celebrex and Bextra.

GSK's Motion to Exclude Dr. Jewell as an expert witness is based on the following criticisms of his report: 1) failure to following scientific methodology in drawing causal inferences from associations; 2) failure to rule out the role of bias, confounding and chance; 3) failure to apply the Bradford–Hill criteria; 4) drawing conclusions about myocardial infarction from data measuring myocardial ischemic events; 5) failure to consider two recent meta-analyses which undermine his conclusions; 6) failure to consistently apply study evaluation criteria; and 7) failure to secure publication of his opinion; and 8) the lack of general acceptance by the relevant scientific community.

*Failure to use proper methodology to draw causal inferences*

***13** The Court's concern in deciding this *Daubert* motion is the methodology used, not the conclusions drawn, by the proposed experts. As noted, the experts are not required to use the best possible methods, but rather are required to use scientifically reliable methods. Plaintiffs and Defendants agree that to conclude that a medication causes an adverse outcome, the epidemiological data must show an association between the use of the medication and the adverse outcome, and that association must not be the result of chance, bias, or confounding. Once the researcher is confident that the association is real, he or she will assess other factors (such as the Bradford–Hill criteria) to draw conclusions about whether the medication which is associated with an outcome actually *causes* the outcome. GSK asserts that Dr. Jewell's methods were unreliable at all three steps. The Court disagrees.

Dr. Jewell's report includes a summary of several studies showing a statistically significant association between Avandia and myocardial infarction (i.e., an association that is unlikely to be found by chance). The Court disagrees with GSK's assertion that Dr. Jewell's opinion relies solely on the results of a single meta-analysis in which the association did not reach statistical significance, because his report clearly indicates a thorough review and consideration of a large number of studies. Dr. Jewell includes a thorough discussion of the methodological flaws in the design of and data collection for studies which do not find such an association, including an explanation about why those studies might be biased towards the null hypothesis (i.e. a statistical finding that the association may be the result of chance), including bias and confounding. While his report does not analyze the studies supporting his conclusions in the same detail, the Court notes that he places his greatest reliance upon those studies that minimize bias and confounding: 1) the RCTs, and particularly those in which the patients and doctors are blind to the study arm to which the patient is assigned, and those where the control arm is given a placebo rather than another active medication; [73] and 2) those studies that statistically or otherwise control for other variables. [74] Therefore, the Court finds that he has given attention to the role of chance, bias and confounding in arriving at his conclusion that there is a real association between Avandia and myocardial infarction, and further finds that he uses consistent criteria to evaluate the possible roles of chance, confounding, and bias both in studies that support and contradict his conclusions.

Although Dr. Jewell relies upon meta-analysis to reach his conclusion, he acknowledges that there are limitations to any meta-analysis. He explains that safety effects of a medication often cannot be determined without combining studies, because individual studies, especially drug efficacy studies as opposed to drug safety trials, are generally underpowered to explore unusual adverse effects, and may also be too short in duration. [75] , [76] He notes that he looked for more than one well-performed meta-analysis to lead to similar and consistent results before drawing his conclusions, to reduce the likelihood that the results were the result of chance, bias or confounding.

***14** GSK also argues that Dr. Jewell failed to consider the Bradford–Hill criteria in drawing his conclusions of causation from the association between Avandia and myocardial infarction. The Court again disagrees, finding that Dr. Jewell addressed many of the Bradford–Hill criteria throughout his report, including temporal relationships (evaluating studies as brief as four weeks and as long as several years), strength of association (which is seen in the confidence interval and the statistical probability of the association being the result of chance), replication of findings by other researchers, specificity of association (e.g., a showing that a similar association is not found for patients taking other drugs in its class), and consistency between studies using different methods (e.g., RCT and observational studies; studies using placebo controls and those using active controls). He notes that he could not assess whether there was a dose response, because there was little variation in the prescribed doses of Avandia. [77] Because he is a mathematician and not a

medical doctor, he did not examine biologically plausible mechanisms for the association.

*Reliance on Studies with Over–Broad Outcome Measures*

GSK objects to Dr. Jewell's reliance on studies with over-broad outcome measures in his report, while Dr. Jewell's report critiques GSK's safety studies, such as RECORD, on the same grounds, stating that GSK's use of an overly broad endpoint dilutes the signal strength for myocardial infarction and biases the results towards the null. [78]

GSK argues that much of the data upon which Dr. Jewell relies for his opinion regarding the causal relationship between Avandia and myocardial infarctions actually combines infarctions with other ischemic events. Some of these events are serious, but others are relatively minor. It is improper, then, to draw conclusions about infarctions from data about a broader category of events. The Court agrees with the need to focus, at this point in the litigation, on whether Avandia causes myocardial infarctions, but finds that Dr. Jewell's report does pinpoint the data on myocardial infarctions when it is possible to do so (e.g., in reviewing the NISSEN and SINGH meta-analyses, and the recent Harvard and Michigan studies), [79] and apparently finds in such data sufficient evidence to support his position. He does not try to extrapolate from the composite outcome data, as GSK argues, but rather looks to studies where myocardial infarctions are themselves measured outcomes. Plaintiffs also note that myocardial ischemic events and myocardial infarctions have the same underlying etiology (loss of oxygen to the heart), and an infarction is simply an ischemic event that deprives the heart of oxygen for a prolonged period of time. Accordingly, the Court does not find that the methods Dr. Jewell used to reach his conclusions were unreliable.

*Ignoring Relevant Data*

GSK argues that Dr. Jewell simply ignores relevant data which does not support his position, and in particular points to two meta-analyses conducted by GSK itself, neither of which has been peer reviewed or published. The Court notes that Dr. Jewell devotes much effort in his report to critiquing studies which do not support his position, including RECORD and the MANUCCI meta-analysis, [80] and also explains why he did not consider the two new meta-analyses performed by GSK to be persuasive. [81] He explains that in the first new meta-analysis, GSK researchers redefined the endpoint events, using an overly broad endpoint rather than focusing on myocardial infarctions, and did not engage in blind adjudication of outcome events. He also notes that the FDA found that study to be less reliable and informative than GSK's original meta-analysis. [82] In the second new meta-analysis, which expanded ICT from a meta-analysis of 42 studies to a meta-analysis of 52 studies, Dr. Jewell explains that a single study, APPROACH, dominated the data from the ten additional studies, as 95 of the 109 new events in the meta-analysis were in the APPROACH data set, and 5 of the 9 new myocardial infarctions occurred in that data set. [83] He found the APPROACH study to be unreliable for two primary reasons: 1) the study used an active medication for the control group, not a placebo; and 2) 76% of participants were on statins at the outset of the trial, whereas in the original studies, baseline statin use ranged from 3–11% in all but one of the 42 trials. [84] The Court is persuaded that Dr. Jewell did not simply ignore relevant data, but rather disregarded that data after finding it scientifically unreliable.

**15 Overall, the Court finds that Dr. Jewell's opinion is supported by his considered interpretation of the scientific data. The Court notes that his conclusions are not at issue at this time, but only his methods. The Court finds Dr. Jewell's methods are scientifically reliable, and accordingly will deny GSK's Motion.

***Conclusion***

Each of Plaintiffs' three experts have consulted an extensive body of epidemiological research to support their conclusions, and evaluated and weighed the quality and usefulness of the various studies. Although the conclusions differ from the conclusions reached by GSK's experts, generally speaking the epidemiological studies relied upon by Plaintiffs' experts are the same studies consulted by GSK and the FDA in their evaluation of the risk profile of Avandia. Plaintiffs' experts arrived at their conclusions that sound scientific evidence supports a causal inference without any speculative leap. They were able to opine to a causal connection between Avandia and myocardial infraction with a reasonable degree of medical or scientific certainty. Therefore, the Court finds that the experts' methods are the product of reliable principles and methods, and the experts had good grounds to reach their conclusions. Differences in conclusions go to the weight

of the evidence, and not to its admissibility. Accordingly, GSK's Motions to Exclude Plantiffs' general causation experts Drs. Brinton, Sniderman and Jewell are denied.

**All Citations**

Not Reported in F.Supp.2d, 2011 WL 13576

Footnotes

1 Doc. No. 734.
2 Doc. No. 736
3 Doc. No. 740
4 *In re TMI Litig.*, 193 F.3d 613, 664 (3d Cir.1999).
5 However, where the scientific community considers the evidence to be inconclusive, a difference of opinion may sometimes undermine the reliability of an expert's conclusion that there is a causal link, and may justify excluding that expert. *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F.Supp.2d 584, 607 (D.N.J.2002), *aff'd* 68 F. App'x 356 (3d Cir.2003).
6 *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 745 (3d Cir.1994); *Holbrook v. Lykes Bros. S.S. Co.*, 80 F.3d 777, 784 (3d Cir.1996).
7 *See, Daubert v. Merrell Dow Pharms. Inc.*, 509 U.S. 579, 590 (1993).
8 *Daubert*, 509 U.S. at 593–94.
9 *In re Diet Drugs Prods. Liab. Litig.*, No. MDL 1203, 2001 WL 454586 at *13 (E.D.Pa. Feb. 1, 2001).
10 No RCT has found a statistically significant association between Avandia and myocardial infarction; the NISSAN and SINGH meta-analyses did find statistically significant associations, as did the majority of the observational studies. The MANNUCCI meta-analysis did not.
11 GSK complains that this study used interim RECORD data and unadjudicated ADOPT data.
12 *Soldo v. Sandoz Pharms. Corp.*, 244 F.Supp.2d 434, 514 (W .D. Pa.2003).
13 GSK cites to five long-term RCTs evaluating the impact of Avandia on atherosclerosis: VICTORY, STARR, APPROACH, PPAR, and HEDBLAD, none of which found an adverse impact, and MARGOLIS which found that Avandia *reduced* the risk of atheroschlerotic disease of the heart by 40% (as statistically significant finding).
14 Brinton Report ("B.R.") at 7.
15 B.R. at 7.
16 B.R. at 9.
17 B.R. at 9.
18 B.R. at 9.
19 B.R. at 10.
20 B.R. at 10.
21 B.R. at 11.
22 B.R. at 11.
23 B.R. at 10–12.
24 B.R. at 14.
25 B.R. at 12–13.
26 B.R. at 14–15.
27 B.R. at 15.
28 B.R. at 16.
29 B.R. at 16.
30 B.R. at 16.
31 B.R. at 17.
32 B.R. at 18.
33 B.R. at 18.
34 B.R. at 20.
35 B.R. at 20–21.

36 B.R. at 21.
37 B.R. at 23.
38 B.R. at 23.
39 B.R. at 23–24.
40 B.R. at 4–5.
41 B.R. at 5.
42 B.R. at 26.
43 Dr. Brinton explains that a second meta-analysis performed by GSK, which included the APPROACH data, did not show a significant increase in cardiovascular disease with Avandia use, but because the APPROACH study recruited higher-risk patients, the data are not as strong as other data.
44 B.R. at 35–6 (discussing the Casscells study).
45 B.R. at 36.
46 B.R. at 19 (citing NISSEN and DORMUTH studies).
47 Doc. No. 734 at 1–3.
48 Doc. No. 734 at 3.
49 Sniderman Report ("S.R.") at 3.
50 Dr. Sniderman characterizes the evidence of this effect as "incontrovertible." S.R. at 3.
51 S.R. at 3.
52 S.R. at 11.
53 S.R. at 11.
54 S.R. at 13.
55 S.R. at 16–18.
56 S.R. at 17.
57 S.R. at 20.
58 S.R. at 7.
59 Doc. No. 740 at 16–19.
60 Doc. No. 740 at 17.
61 S.R. at 13–14.
62 S.R. at 21.
63 S.R. at 21.
64 S.R. at 26.
65 S.R. at 28–29.
66 S.R. at 28.
67 S.R. at 28.
68 S.R. at 30.
69 S.R. at 31.
70 S.R. at 31.
71 S.R. at 33.
72 S.R. at 33.
73 Jewell Report ("J.R.") at 10.
74 E.g., J.R. at 35.
75 J.R. at 5, 9.
76 Even studies such as RECORD, which are designed to test safety, may be underpowered if a large number of subjects drop out of their treatment group (as occurred in RECORD).
77 J.R. at 32.
78 J.R. at 8–9, 24.
79 J.R. at 11, 23, 36, 38.
80 J.R. at 24–32.
81 J.R. at 19–23.
82 J.R. at 20.

83 J.R. at 21.
84 J.R. at 22.

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